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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/555,343	11/01/2005	Akira Kato	1089.0590000/MAC	4524

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EXAMINER	
RICCI, CRAIG D	

ART UNIT	PAPER NUMBER
1614	

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02/19/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/555,343	KATO ET AL.	
	Examiner	Art Unit	
	CRAIG RICCI	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 September 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5-10,13-18 and 21-27* is/are pending in the application.

4a) Of the above claim(s) *16-18 and 21-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2, 5-10, 13-15 and 24-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/19/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. The amendments filed 09/19/2008 were entered.

2. The rejection of claims 1-15 under 35 U.S.C. 102(b) has been withdrawn in view of Applicant's amendment.

Response to Arguments

3. Applicants' arguments, filed 11/28/2008, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. **Claims 1 and 5-7 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Banker and Rhodes* (Modern Pharmaceutics, Fourth Ed., 2002, Pages 394 and 399), *Fumihiro et al* (JP Application 62-288534, provided by Applicant), *Hunik* (WO 2000/37669), *Makino et al* (US 4,948,788), *Craig et al* (Int J Pharmaceut 179:179-207, 1999), and *Kim et al* (J Pharm Sci 87:931-935, 1998)**.

7. The following rejection is necessitated by amendment.

8. Instant claim 1 as amended is drawn to a freeze-dried preparation comprising methycobalamin and an excipient wherein the excipient comprises at least one sugar (for example sucrose or lactose) or at least one sugar alcohol (for example, mannitol) in an amorphous state and present in an amount that is at least 20% by weight based on the total weight of the excipient. More specifically, as recited by instant claim 7, the excipient comprises at least one sugar **and** at least one sugar alcohol.

9. As taught by *Banker and Rhodes*, "[m]any drugs are too unstable – either physically or chemically – in an aqueous medium to allow formulation as a solution, suspension, or emulsion. Instead, the drug is formulated as a dry powder" (Page 394, Column 2). It is generally known that vitamins, including vitamin B_{12}, (of which methylcobalamin is the active form) are not very stable and that degradation is observed on storage. Specifically, *Hunik* discloses that "methylcobalamin… [is] known to be unstable to light in isolated form and [is] easily transformed to hydroxycobalamin

in aqueous solution" (Page 1, Lines 23-26). However, *Fumihiro et al* teach stable freeze-dried preparations comprising vitamin B_{12} (Abstract).

10. Accordingly, a freeze-dried preparation comprising methylcobalamin would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made. The skilled artisan, recognizing the instability of methycobalamin (as taught by *Hunik*) would have been motivated to formulate methylcobalamin as a dry powder (as taught by *Banker and Rhodes*), specifically by freeze-drying (as taught by *Fumihiro et al*). In view of *Fumihiro et al*, which teach stable freeze dried preparations comprising vitamin B_{12} (and considering that methylcobalamin is the active form of vitamin B_{12}) the skilled artisan would have reasonably predicted that a freeze-dried preparation comprising methylcobalamin would possess enhanced stability and thus overcome the problems disclosed by *Hunik*.

11. Additionally, it would have been *prima facie* obvious to include the excipients as recited in claims 1 and 7 in a freeze-dried preparation comprising methylcobalamin. As disclosed by *Craig et al*, "cryoprotectants are materials which are commonly added during the freeze drying process in order to afford protection of the drug from degradation… The most commonly used cryoprotectants are sugars, although polymers and amino acids may also be used" (Page 202, Columns 1-2). Furthermore, *Makino et al* (US 4,948,788) teach a freeze-dried preparation comprising vitamin D_3 (which, like methylcobalamin, is a vitamin that is unstable to light (Column 1, Lines 23-24)) and an excipient (Abstract) having good stability (Column 2, Line 8). More specifically, *Makino et al* state that "excipients usable in the present invention may include amino acids,

monosaccharides, disaccharides..." [and] "[m]onosaccharides and disaccharides may include mannitol… lactose… and the like" (Column 2, Lines 35-39). Thus, in view of *Craig et al*, the skilled artisan would have found it obvious to include excipients, such as sugars, in the freeze-dried preparation with the reasonable expectation that their inclusion would protect the methylcobalamin from the possibility of degrading during freezing. More specifically, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to include mannitol and lactose (or the like) in view of *Makino et al* which teach that the recited excipients are known excipients useable in stable freeze-dried preparations comprising light-unstable vitamins. Accordingly, the skilled artisan would have included mannitol and lactose (or the like) in the recognition that degradation of any drug is a concern during freeze-drying and that sugars are well known excipients used as cyroprotectants during freeze-drying drug preparations (in view of *Craig et al*) and in the further recognition that mannitol, lactose and the like are usable excipients in freeze-dried preparations comprising vitamins (in view of *Makino et al*). Thus, the person of ordinary skill in the art would have reasonably predicted that the inclusion of mannitol and lactose (or the like) would successfully provide cryoprotection during freeze-drying of a vitamin, such as methylcobalamin. As stated by the Court in *KSR International Co., v. Teleflex Inc.*, 82 USPQ2d 1385 (2007) "when a patent 'simply arranges old elements with each performing the same function it had been known to perform' and yields no more than one would expect from such an arrangement, the combination is obvious" quoting *Sakraida v. AG Pro, Inc.*, 189 USPQ 449 (1976). In the instant case, the recited

excipients are known in the art as cryoprotectants in freeze dried preprations, including freeze-dried vitamin preparations. Thus, the arrangement of old excipients with each performing the same function of cryoprotection that they had been known to perform and yielding no more than one would expect from such an arrangement, is *prima facie* obvious. That is, the skilled artisan would have found it *prima facie* obvious to combine known prior art elements according to known methods to yield predictable results.

12. Furthermore, it would have been *prima facie* obvious to include the excipients "wherein at least one or more of said sugar or said sugar alcohol… is in an amorphous state… at least 20% by weight" as recited by instant claim 1. *Banker and Rhodes* teach mannitol as a common excipient in freeze-dried preparations and disclose that "crystallization of mannitol during heating is believed to be the underlying cause of vial breakage in mannitol-based formulations" (Page 399, Column 1). Although Banker and Rhodes are discussing freeze-dried preparations comprising proteins, the skilled artisan would similarly wish to avoid vial breakage during heating of freeze-dried mannitol-based vitamin formulations. Accordingly, it would have been prima facie obvious to avoid crystallization by providing amorphous excipients. In order to achieve this, the skilled artisan would turn to *Kim et al* which teach that freeze-dried preparations comprising mannitol **and** a cosolute such as sucrose or lactose provide an amorphous excipient (entire document). More specifically, *Kim et al* report that "the relative concentration threshold above which crystalline mannitol is detected by X-ray diffraction is about 30% (w/w)" and that that "the glass transition decreases markedly as the relative concentration of mannitol increases" (Page 933, Column 2). Accordingly, in

order to avoid vial breakage, the skilled artisan would have found it *prima facie* obvious to include mannitol and a cosolute such as sucrose or lactose. Furthermore, since *Kim et al* disclose that "the relative concentration threshold above which crystalline mannitol is detected by X-ray diffraction is about 30% (w/w)" (Page 933, Column 2), the skilled artisan would have found it *prima facie* obvious to include at least 70% sucrose or lactose (w/w) in the excipient (see also *Kim et al*, Page 934, Table I). The skilled artisan would have been motivated to include sucrose or lactose in an amount that is at least 20% by weight (as recited by the instant claim), more specifically at least 70% by weight, in order to maintain mannitol in an amorphous state and thus avoid or reduce the likelihood of vial breakage.

13. Instant claims 5-6 and 24 are drawn to the preparation of claim 1 further comprising a pH adjuster (claim 5) and/or an antioxidant (claims 6 and 24). *Makino et al*, which is drawn to a stabilized freeze-dried preparation comprising vitamin D_3 (which, like methylcobalamin, is a vitamin that is unstable to light in aqueous compositions) and an excipient, teach the inclusion of antioxidants and buffering agents (Column 3, Lines 20-31) in the preparation. Accordingly, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to further include a pH adjuster and an antioxidant because, in view of *Makino et al* and in view of *KSR International Co. v. Teleflex, Inc* as discussed above, the arrangement of old ingredients (antioxidants and pH buffers) with each performing the same function of enhancing stabilization that they had been known to perform and yielding no more than one would expect from such an arrangement, is *prima facie* obvious. That is, the skilled artisan

would have found it *prima facie* obvious to combine known prior art elements according to known methods to yield predictable results.

14. **Claims 2, 8-10, 13-15, and 25-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Banker and Rhodes* (Modern Pharmaceutics, Fourth Ed., 2002, Pages 394 and 399), *Fumihiro et al* (JP Application 62-288534, provided by Applicant), *Hunik* (WO 2000/37669), *Makino et al* (US 4,948,788), *Craig et al* (Int J Pharmaceut 179:179-207, 1999), and *Kim et al* (J Pharm Sci 87:931-935, 1998) as applied to claim 1, in view of *FDA Guide to Inspections of Lyophilization of Parenterals* (available online at http://www.fda.gov/ora/inspect_ref/igs/lyophi.html as of February 28, 1997) and *West* (Science 107:398, 1948).**

15. The following rejection is necessitated by amendment of claim 1.

16. Instant claim 2 is drawn to the freeze-dried preparation of claim 1 wherein the methylcobalamin is also in an amorphous state. The *FDA Guide to Inspections of Lyophilization of Parenterals* states that one problem associated with lyophilized powders is poor solubility, "[i]ncreased time for reconstitution at the user stage may result in partial loss of potency if the drug is not completely dissolved, since it is common to use in-liner filters during administration to the patient" (Page 14, Paragraph 2). As taught by *Craig et al*, amorphous drugs possess enhanced dissolution profiles compared to crystallized drugs (Page 191). And, furthermore, *West* teaches amorphous vitamin B_{12} injections (Entire document) which comprises methylcobalmin (as evidenced by *Hunik*, discussed above), thus indicating the feasibility of formulating amorphous methylcobalamin to one of ordinary skill in the art at the time the invention

was made. Accordingly it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to include methylcobalamin in an amorphous state. The skilled artisan would have been motivated to do so in order to ensure adequate dissolution and thus overcome the problem associated with lyophilized drugs taught by the *FDA Guide* and, in view of West, would have recognized the feasibility of formulation an amorphous methylcobalamin. Furthermore, the teaching that the amorphous state may reduce chemical and physical stability of the preparation would not dissuade the skilled artisan in view of *Craig et al* which specifically state that "the onset of the devitrification process may be so slow so as to be effectively irrelevant within the storage time of a product" (Page 180, Column 1).

17. Instant claims 8-10, 13-15, and 25-27 are all drawn to a freeze dried preparation comprising methylcobalamin and an excipient wherein the freeze dried preparation is obtained by a specific process. As stated by MPEP 2113:

> **PRODUCT-BY-PROCESS CLAIMS ARE NOT LIMITED TO THE MANIPULATIONS OF THE RECITED STEPS, ONLY THE STRUCTURE IMPLIED BY THE STEPS**
>
> "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted)

. In the instant case, the instantly claimed product in the product-by-process claim is obvious from a product of the prior

art as previously discussed in view of *Banker and Rhodes*, *Fumihiro et al*, *Hunik*, *Makino et al*, *Nail et al*, *Kim et al*, *FDA Guide to Inspections of Lyophilization of Parenterals*, *Craig et al* and *West*. Accordingly, the obvious product as obtained by the process recited by claims 8-10, 13-15, and 25-27 is rejected as *prima facie* obvious in view of *In re Thorpe*.

Conclusion

The new ground(s) of rejection presented in this Office action were necessitated by Applicant's amendments to the claims. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CRAIG RICCI whose telephone number is (571) 270-5864. The examiner can normally be reached on Monday through Thursday, and every other Friday, 7:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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